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UNITED STATES PATENTS QUARTERLY

Bristol-Myers Co. v. U.S. International Trade Commission

No. 89-1530

U.S. Court of Appeals Federal Circuit

15 U.S.P.Q.2D (BNA) 1258

Decided December 8, 1989

CASE HISTORY and DISPOSITION: Appeal from the U.S. International Trade Commission.

Complaint by Bristol-Myers Co., alleging unfair competition in the importation of certain crystalline cefadroxil monohydrate that infringes its patent no. 4,504,657. From final determination denying request for temporary relief under 19 USC 1337(e), complainant appeals. Reversed.

[Editor's Note: The Court of Appeals for the Federal Circuit has designated this opinion as one that "has not been prepared for publication in a printed volume because it does not add significantly to the body of law and is not of widespread legal interest. It is a public record. It is not citable as precedent."]

HEADNOTES:
PATENTS

[1H]** 1. Patentability/Validity - Construction of claims (115.03)

X-ray powder diffraction pattern is accepted "fingerprint" for identification of crystal structure.

[2H]** 2. Patentability/Validity - Obviousness - Evidence of (115.0906)

In determining obviousness of new chemical structure, consideration is given, as appropriate on particular facts, to motivation or suggestion in prior art to produce new structure, to problem confronting inventor, to nature of new structure as compared with prior art, and to any other criteria as may arise in any particular case.

[3H]** 3. Patentability/Validity - Obviousness - In general (115.0901)

Correct inquiry under *35 USC 103* is not whether new monohydrate could have been produced by manipulation of other cefadroxil processes, once existence of new monohydrate was known, but whether it would have been obvious to make new monohydrate based on prior art.

[4H]** 4. U.S. International Trade Commission - Procedure (155.02)

Purpose of preliminary relief in *19 USC 1337* actions is to preserve intellectual property rights during course of litigation, and U.S. International Trade Commission should not refrain from granting provisional relief when requirements for such relief have been met.

[5H]** 5. U.S. International Trade Commission - In general (155.01)

Principle public policy implemented by *19 USC 1337* is protection of valid patent and other intellectual property rights.

Particular patents - Chemical - Drugs

4,504,657, Bouzard, Weber, and Stemer, cephadroxil monohydrate, denial of temporary relief under *19 USC 1337* reversed.

CLASS-NO: 115.03, 115.0901, 115.0906, 155.01, 155.02

JUDGES: Before Cowen, senior circuit judge, and Rich and Newman, circuit judges.

OPINIONBY: Newman, J.

OPINION:
Bristol-Myers Company appeals the final determination of the United States International Trade Commission in Investigation No. 337-TA-293, In re Certain Crystalline Cefadroxil Monohydrate, issued June 13, 1989, denying Bristol-Myers' request for temporary relief under *19 U.S.C. 1337*(e) (1988). We reverse.

OPINION Bristol-Myers alleged unfair acts in violation of *19 U.S.C. 1337* (1988), based on infringement of United States Patent No. 4,504,657 by certain crystalline cefadroxil monohydrate imported into the United States, and requested that the accused goods be excluded pendente lite, as authorized by *19 U.S.C. 1337*(e)(3) (1988). Recently enacted *19 U.S.C. 1337*(e)(3) (1988) codified the Commission's authority with respect to preliminary relief:

The Commission may grant preliminary relief under this subsection or subsection (f) to the same extent as preliminary injunctions and temporary restraining orders may be granted under the Federal Rules of Civil Procedure.

On appellate review we apply the same standard as is applied to similar rulings of district courts, with appropriate deference to factual findings of the Commission. We determine whether the Commission, in its grant or denial of preliminary relief, abused its discretion, committed an error of law, or seriously misjudged the evidence. See *H.H. Robertson, Co. v. United Steel Deck, Inc., 820 F.2d 384, 387, 2 USPQ2d 1926, 1927 (Fed. Cir. 1987); Smith Int'l, Inc. v. Hughes Tool Co., 718 F.2d 1573, 1579, 219 USPQ 686, 691* (Fed. Cir.), cert. denied, *464 U.S. 996 [220 USPQ 385]* (1983). Questions of law are reviewed for correctness. *Surface Technology, Inc. v. United States Int'l Trade Comm'n, 801 F.2d 1336, 1340 n.7, 231 USPQ 192* , 195 n.7 (Fed. Cir. 1986). Factual findings, including factual underpinnings of legal conclusions, are reviewed to determine whether they are supported by substantial evidence. *Tandon Corp. v. United States Int'l Trade Comm'n, 831 F.2d 1017, 1019 4 USPQ2d 1283, 1284-85 (Fed. Cir. 1987).* See *5 U.S.C. 706* (2)(E) (1988).

Background The disputed product is a certain crystal form of cefadroxil monohydrate. Cefadroxil is an antibiotic of the cephalosporin family, and is in wide use due to its effectiveness against bacteria that are resistant to penicillin.

Cefadroxil was discovered by Leonard Crast, and is described and claimed in United States Patent No. 3,489,752, issued on January 13, 1970 and assigned to Bristol-Myers Company (Crast I). In Crast I the cefadroxil product is not described in any particular crystal form or degree of hydration. Its superior antibiotic properties were recognized, but the product was unsuitable for clinical studies because it could not be obtained in sufficiently pure form.

After further research, Crast and a co-worker Gottstein in 1972 produced a dimethylformamide (DMF) solvate that was a relatively pure form of the antibiotic, but was still unsuitable for human use because of toxicity of the DMF. Crast and Gottstein developed a process for removing the DMF, called the "slurrying" process, yielding a crystalline cefadroxil monohydrate that was sufficiently pure for clinical use. This crystalline monohydrate and the slurrying process are disclosed in United States Patent No. 3,985,741, issued on October 12, 1976 ("Crast II"), although the crystal form is not claimed. The product is called "the Gottstein monohydrate" in this action.

Bristol-Myers chemists Bouzard and Weber, assigned the task of developing a commercial process, developed a different process for removing the DMF from the DMF solvate, using acetonitrile and water. This process produced a further, different crystalline form of cefadroxil monohydrate, called "the old monohydrate" in this action. Subsequently Bouzard

discovered that by changing the solvent system he could produce a crystalline trihydrate. The trihydrate was selected for pilot plant production, and Bristol-Myers proceeded with production and clinical trials.

Go to Headnotes **[**1R]** [1] Some ten months thereafter, in the course of certain aqueous stability tests of the cefadroxil trihydrate, Bouzard observed the appearance of yet another crystalline form of cefadroxil. This form is called the "new" or "Bouzard monohydrate" in this **[*1260]** action. Since that time, Bristol-Myers has been unable to reproduce the trihydrate form. The Bouzard monohydrate and the process for preparing it are disclosed in United States Patent No. 4,504,657, issued March 12, 1985, assigned to Bristol-Myers (the '657 or Bouzard patent). The product is claimed in the '657 patent as a specific crystalline cefadroxil monohydrate, identified by its X-ray powder diffraction pattern, an accepted "fingerprint" for crystal structure.

The Bouzard monohydrate is described as an improvement over other forms of cefadroxil due to its stability, and its higher bulk density which enables production of smaller pills. The Chief Administrative Law Judge ("ALJ") found that its doses have longer effectiveness than other forms; a finding that the Commission adopted but now criticizes in its brief.

The six intervenors, all manufacturers or importers and distributors of cefadroxil in the patented crystalline form, participated in this appeal, as in the action before the Commission.

On the expedited schedule contemplated in *19 U.S.C. 1337*(e)(2) (1988), the ALJ held an evidentiary hearing on the requested temporary exclusion. We shall discuss the principal issues considered in denial of preliminary relief.

Anticipation The ALJ found that the Bouzard monohydrate was not anticipated by the disclosure in Garbrecht United States Patent No. 3,781,282, issued December 25, 1973, assigned to Eli Lilly & Co. The intervenors argue that the ALJ erred.

Garbrecht describes a process for producing cephalosporin hydrates, and states in Example 7 that the cephalosporin process can be performed using different starting materials to prepare a cefadroxil product. Garbrecht does not show any specific crystalline or hydrated form of cefadroxil. There was significant agreement that Example 7 as written does not produce any crystalline monohydrate product whatsoever. At oral argument Bristol-Myers said it produces "gunk". It was vigorously disputed as to what crystal forms of cefadroxil could be or would be produced by modification of Garbrecht Example 7.

Anticipation is a factual determination and, like other Commission findings of evidentiary fact, is reviewed on the substantial evidence standard. *Tandon, 831 F.2d at 1019, 4 USPQ2d at 1284-85* . We have reviewed the arguments of all sides in light of the record, and conclude that substantial evidence supports the ALJ's ruling that the Bouzard monohydrate was not anticipated in the Garbrecht reference. See *Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920* (Fed. Cir.), cert. denied, *110 S.Ct. 154 (1989)* (for anticipation the claimed invention must be described in a single prior art reference).

The parties adduced evidence as to various modifications of Example 7. This evidence was treated by the ALJ as pertinent to section 103, not section 102. These arguments are pressed by the intervenors as related to inherency as well as to obviousness. The argument of inherency is negated by the ALJ's finding that various crystal forms were obtained, depending on the process modifications made. Substantial evidence supports the ALJ's finding that the Bouzard monohydrate is not inherently formed in the Garbrecht or Crast processes. We apply the principle stated in *In re Chapman, 357 F.2d 418, 422, 148 USPQ 711, 714 (CCPA 1966):*

Nor can we agree that appellant's compositions are unpatentable because such a process "would inherently yield" a product substantially the same as that claimed, since that position implies that any and all products of obvious processes are unpatentable by reason of their being "inherent" results of those processes. The issue is simply obviousness of a composition of matter[.]

Obviousness The Commission held that there was not substantial likelihood that the validity of the Bouzard patent would be sustained under *35 U.S.C. 103.* For purposes of this appeal, Bristol-Myers states that it accepts the ALJ's factual findings that the process steps necessary to make the Bouzard monohydrate were within the skill of the art. We

take this as acceptance, for purposes of this appeal, of the ALJ's pertinent findings as to the Graham factors [*Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966)]:* the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill, and secondary considerations. We thus review the Commission's conclusion of obviousness for correctness as a matter of law, *Surface Technology, 801 F.2d at 1341, 231 USPQ at 196* , although we observe that all sides continue to debate the factual premises as well as their significance.

Go to Headnotes **[**2R]** [2] In determining the obviousness vel non of a new chemical structure, consideration is **[*1261]** given, as appropriate on the particular facts, to the motivation or suggestion in the prior art to produce the new structure; to the problem confronting the inventor; to the nature of the new structure as compared with the prior art; and to any other criteria as may arise in any particular case. The richness of precedent shows the variety of factual considerations that may arise in deciding whether the invention as a whole would have been obvious to one of ordinary skill in the field of the invention, at the time the invention was made.

The intervenors introduced evidence that several highly skilled chemists, by chemically modifying Garbrecht Example 7, produced the Bouzard monohydrate. Bristol-Myers adduced contradictory evidence, that Dr. Micetich did not produce the Bouzard monohydrate in his two experiments modifying Example 7 as suggested by the patent examiner; and that another experienced chemist, highly motivated to do so, nonetheless failed to make the new monohydrate by modifying Example 7. (These chemists all had Ph.D. degrees; the level of ordinary skill found by the ALJ was an undergraduate degree in chemistry and one year's experience with cefadroxil chemistry.)

As for Crast II, the record shows that experts for Biocraft, as well as for Bristol-Myers, readily produced, following Crast Example 6, a different monohydrate from that of Bouzard, while Professor Just produced the Bouzard monohydrate by changing the Crast procedure. It was undisputed that the product obtained at the time the Crast work was initially done was not the Bouzard monohydrate but the Gottstein monohydrate.

The ALJ found as fact that:

[T]here was a need for and motivation to prepare various commercial forms of cefadroxil, including crystalline cefadroxil monohydrate... Yet a number of experienced chemists did not obtain the new monohydrate. Mr. Gottstein, an experienced Bristol cephalosporin chemist, made a cefadroxil hydrate, but not the new monohydrate. Eli Lilly, which owned the Garbrecht patent did not make the new monohydrate.

Go to Headnotes **[**3R]** [3] Bristol-Myers' position is that the ALJ applied an improper legal standard, in determining that the Bouzard invention would have been obvious in terms of *35 U.S.C. 103.* The ALJ stated, with respect to the Garbrecht reference:

[T]he issue under Section 103 is whether one with ordinary skill in the art in April of 1976 could have produced the cefadroxil monohydrate of the '657 patent (the "new cefadroxil monohydrate" or the "Bouzard monohydrate") by following the teachings of the Garbrecht patent as a whole, and modifying Example 7 of Garbrecht only to the extent that those modifications would have been within the skill of one with ordinary skill in the art at that time. [Emphases added.]

The ALJ applied the same legal theory to the Crast II reference:

One with ordinary skill in the art in 1976 who used what is taught in Example 6 of the Crast patent could have made the new monohydrate of claim 1 of the '657 patent by making only minor adjustments to the procedure, adjustments that would have been well within his skill. [Emphases added.]

The law of 103 requires a quite different inquiry from that conducted by the ALJ. The correct inquiry is not whether the Bouzard monohydrate could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

It is insufficient that the prior art shows methods that some (but not all) chemists were able to modify, to produce the Bouzard crystalline form. There must be a suggestion or teaching in the prior art that the Bouzard crystal structure could or should be made, whether by manipulation of the Garbrecht or Crast II processes, or by any other process. In factual and legal point is *In re Cofer, 354 F.2d 664, 668, 148 USPQ 268, 271 (CCPA 1966),* wherein the court held that a new crystalline form of a compound would not have been obvious absent evidence that "the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form". See also *In re Grose, 592 F.2d 1161, 1167-68, 201 USPQ 57, 63 (CCPA 1979),* wherein the court stated that different crystal forms of zeolites would not have been structurally obvious one from the other, unless there was some chemical theory supporting such a conclusion. See *In re Irani, 427 F.2d 806, 808-09, 166 USPQ 24, 26 (CCPA 1970)* (holding the crystalline anhydrous form of a known chemical compound not obvious).

There is no suggestion in the prior art that the processes of Garbrecht and Crast if modified would be reasonably expected to produce the Bouzard monohydrate. The ALJ discussed, and apparently gave weight to, the absence of an experiment on behalf of Bristol-Myers in which the amount of acid used **[*1262]** in Garbrecht's Example 7 was increased. The ALJ found that by 1983, during the prosecution of the Bouzard patent application, Bristol-Myers scientists knew that hydrochloric acid could remove the Garbrecht protective tert. -butoxycarbonyl group. This, however, can not impart retrospective obviousness to April 1976, when the Bouzard discovery was made in a quite different way, and at which time both Garbrecht and Crast had failed to make it by the processes then in use, which produced other forms of cefadroxil. See *In re Grabiak, 769 F.2d 729, 733, 226 USPQ 870, 872 (Fed. Cir. 1985)* (rejecting the argument that a new chemical compound would have been obvious because it was not inconceivable to make the structural modification made by the applicant); *In re Gyurik, 596 F.2d 1012, 1018, 201 USPQ 552, 557 (CCPA 1979)* (one must consider the practical motivation of one of ordinary skill to make a new compound, in light of the properties or uses the compound would be expected to have if made); and compare *In re O'Farrell, 853 F.2d 894, 902, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988)* (holding that the claimed invention would have been obvious because the reference contained detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence that the modification would be successful).

Indeed, the ALJ found as fact that "the inventors named in the [Bouzard] patent had been working for about two years with cefadroxil before Dr. Weber accidentally obtained the trihydrate that led to the new monohydrate." We once again are reminded of the perils of hindsight analysis, wherein that which was achieved after long effort, or perhaps serendipitously, is with hindsight deemed obvious. See, e.g., *Panduit Corp. v. Dennison Mfg. Corp., 774 F.2d 1082, 1090, 227 USPQ 337, 342 (Fed. Cir. 1985),* vacated on other grounds, *475 U.S. 809 [229 USPQ 478]* (1986) (remarking on "the insidious and powerful phenomenon known in patent law as the use of hindsight").

The ALJ found that two scientists who "may have had more than ordinary skill in the art ... did not try to do what the others tried to do in their first or second efforts to make Garbrecht Exhibit [sic: Example] 7". Yet the ALJ concluded that "one with ordinary skill in the art who was trying to produce a crystallized cefadroxil monohydrate using Example 7 of the Garbrecht patent could have made the [Bouzard product] by making adjustments to the procedures taught in Garbrecht, adjustments that would have been within the skill of someone with ordinary skill in the art in 1976." Accepting this conclusion as factually correct, it is irrelevant to whether the Bouzard discovery would have been obvious in terms of 103. The question before the Commission was not whether the Bouzard crystal form could have been duplicated with experimentation or with even minor chemical process changes; the question was whether this new crystal form, as a composition of matter, would have been obvious from the teachings of the prior art.

The patentability of a new chemical structure is independent of how it is made. See, e.g., *In re Hoeksema, 332 F.2d 374, 377, 141 USPQ 733, 736 (CCPA 1964)* (product patentable, although the process was unpatentable for obviousness). Expert witnesses for both sides, Dr. Dunitz for the intervenors and Dr. Baldwin for Bristol-Myers, agreed that the Bouzard crystal structure was not predictable from the known forms of cefadroxil.

The ALJ explained that there were no differences between the teachings of the Garbrecht or Crast II patents and the Bouzard patent "that would have prevented one with ordinary skill in the art from making" the new monohydrate using the teachings of the references with minor modifications. This statement sheds light on the ALJ's error of law, affirmed by the Commission. There must be an affirmative suggestion or teaching in the prior art whereby it would have been obvious to make the new monohydrate; not simply the absence of obstacle. No such suggestion or teaching has been shown.

Applying the correct legal criteria to the determination of obviousness, the Commission erred in holding that it was likely that the claims to the Bouzard monohydrate would be proved invalid. That holding is reversed.

Enforceability The ALJ also found that the Bouzard patent had not been shown to be unenforceable for inequitable conduct, and that such showing was unlikely to be made at full hearing. This holding is challenged by the intervenors, but has not been shown to be in error, or that the factual findings as to materiality and intent were unsupported by substantial evidence.

The Temporary Exclusion Order Go to Headnotes **[**4R]** [4] The purpose of preliminary relief in Section 1337 actions is to preserve the intellectual property right during the course of litigation. It recognizes that the harm of infringement is not readily subject to full **[*1263]** monetary remedy, due to the inexorable expiration of the property right. Congress enacted new expedited proceedings for preliminary relief in 1988 because "[e]xperience under the present statute has shown that the Commission sometimes provides temporary relief to complainants too late to benefit them." H.R. Rep. No. 40, 100th Cong., 1st Sess., pt. 1, at 159 (1987); accord, S.Rep. No. 71, 100th Cong., 1st Sess. 131 (1987). This legislative history prescribes that the Commission should not refrain from granting provisional relief when the requirements therefor have been met.

It is not necessary today to ponder the sweep of the analogy to district court practice that is now codified at *19 U.S.C. 1337*(e)(3), and in the regulations at 19 C.F.R. 210.24(e)(1), (9) (1988). Nor need we consider whether the standard for granting or denying temporary exclusion orders was intended by Congress to be weighted against the patentee in 1337 actions, as the ALJ reports. The case at bar does not require so fine a balance.

In this case infringement was admitted or reasonably shown as to all the respondents. The ALJ found irreparable harm to Bristol-Myers, and that the respondents had not proved that they would be harmed by the requested temporary relief. The ALJ also found that the public interest favors lower priced generic drugs. All factors must be considered. *H.H. Robertson, 820 F.2d at 390, 2 USPQ2d at 1930 .*

Go to Headnotes **[**5R]** [5] As discussed in *Smith Int'l, 718 F.2d at 1580-81, 219 USPQ at 692* , "[c]ourts faced with strong showings of validity and infringement ... have found irreparable harm from continued infringement of a valid patent." While the ALJ found that the public interest in cheaper drugs outweighed any adverse effect on Bristol-Myers, we believe that the analysis is more complex than here made. The policy considerations governing the right of a patentee to exclude infringers are embodied in the patent laws, and it is the protection of valid patent and other intellectual property rights that is the principal public policy implemented by 1337. This policy is reinforced by the recent amendments to *19 U.S.C. 1337*(e), designed, as we have noted, to facilitate preliminary relief.

The ALJ, holding that it was likely that the Bouzard patent would be held invalid, denied the requested TEO. We review this ruling in light of our holding that the validity of the Bouzard patent is likely to be sustained. Applying the established jurisprudence, see *H.H. Robertson Co., supra ; Smith International, supra,* we conclude that the Commission exceeded its discretionary authority, committed an error of law, and seriously misjudged the evidence. The refusal to grant temporary relief in this case is reversed. See *5 U.S.C. 706*(1), (2) (1988).